Remarks

Claims 13, 14 and 16-27 are pending and under consideration after the cancellation of claims 1-12 herein. Claim 15 is cancelled. Claim 16 is amended to change its dependency to claim 13 after the cancellation of claim 15 (with support in claims 13 and 15 from which claim 16 as filed depended). Claims 20 and 22 are amended to recite "wherein the lipidated PsaA is recombinantly produced in a High Five cell" as supported at page 27, lines 3-4, 9-11 and 19-20, and page 28, lines 4-6 (PCT publication), and as previously considered in claims 27-29). Thus, claims 28 and 29 are canceled. Claims 27 is amended to delete "high five" and insert therefor "High Five." This is merely the correction of a typographical error of a previously considered limitation. "High Five" is supported at page 27, lines 3-4, 9-11 and 19-20, and page 28, lines 4-6 (PCT publication). Since the present amendments present no new issues and require no additional search, their entry in response to this Office Action is believed to be merited. Thus, reconsideration of the amendments and allowance of all the claims are respectfully requested.

Rejection Maintained

Claims 20-24 remain rejected as allegedly lacking enablement for vaccination with any/all preparations of the lipidated PsaA for reasons of record. In one aspect, the rejection is based on the fact that applicant's examples in the specification do not specify a mode of administration such that the enablement of intranasal administration cannot be accurately assessed.

In this regard, applicants note that claim 20 is not limited to intranasal administration. In fact there is ample evidence that many modes of administration of PsaA are effective for

immunizing the recipient against S. pneumoniae. The following references followed the teaching of the present invention regarding the administration (nasal, subcutaneous, parenteral, etc.) of lipidated PsaA, and the making of the lipidated peptide, and they confirm the results of the present examples. The minor differences from paper to paper are differences in routine selection criteria. The unifying theme in all of these references is that intranasal administration of PsaA has an immunizing effect.

There are numerous publications from the present inventors and others that confirm applicants' teaching that intranasal administration of PsaA is an effective route for immunizing the recipient against *S. pneumoniae*. For example De et al., Vaccine 18 (2000): 1811-1821, describes E. coli-expressed **OspA lipidated PsaA** immunized against *S. pneumoniae* (reduced bacterial carriage) when intranasally administered to mice (see abstract, page 1814, right column, and section 3.4 bridging pages1817 and 1818, Exhibit 1). Briles et al., Vaccine 19 (2001):S87-S95, describes immunization of mice by intranasal administration of **lipidated PsaA** (see page S90, left column, Exhibit 2). The reference also teaches that lipidated PsaA has been able to largely eliminate carriage with pneumococci (see page S89, right column, Figure 2 and Table 4). Briles et al., Infect. Immun. 2000; 68:796-800, describes the elicitation of antibodies in serum and saliva, decrease in carriage and significant protection against *S. pneumoniae* following intranasal administration of recombinant **OspA lipidated PsaA** (see page 797, Exhibit 3). These references validate the efficacy of intranasal administration of lipidated PsaA to immunize animals against *S. pneumoniae*.

There are also references that confirm the present applicants' teaching of other modes of administration of lipidated PsaA. Although there are differences in routine particulars in these experiments, the unifying theme is that PsaA can immunize against carriage when administered using divergent modes of administration. For example De et al., Vaccine 18 (2000): 1811-1821, describes E. coli-expressed **OspA lipidated PsaA** immunized against *S. pneumoniae* (reduced bacterial carriage) when parenterally administered to mice (see section 3.4 bridging pages1817 and 1818, Exhibit 1). De et al., Pathobiology 1999: 67:115-122, describes the administration of sf9- and H5-produced **non-lipidated** PsaA by subcutaneous injection to adult mice. No difference between these two versions is noted in terms of protection against *S. pneumoniae* in adult mice (abstract and Page 120, left column, Exhibit 4). In passive immunization experiments, infant mice were immunized by subcutaneous injection (see page 118, left column). Although the De et al. 1999 reference does not use lipidated PsaA, it is still relevant to the issue of effective administration, because there is no scientific basis to believe that the efficacy shown with the non-lipidated protein would not be repeated with the lipidated version.

Not only does the literature validate applicants' teaching that intranasal administration is effective, it also validates the efficacy other modes of administration. In the absence of specific scientific evidence to the contrary the Office should accept applicants' teaching in the specification and claims regarding administration of lipidated PsaA. Thus, claims 20 and 21 are both enabled.

A further basis for the present rejection is the Office's position that only High Five cell-produced lipidated PsaA is enabled for immunization against *S. pneumoniae*. While not

conceding this point, applicants have amended claims 20 and 22 to recite "High Five-produced recombinant lipidated PsaA." This amendment is supported at page 27, lines 3-4, 9-11 and 19-20, and page 28, lines 4-6 (PCT publication).

Applicants note that claims 22-24 recite a composition of matter. Thus, enablement requires the teaching of how to make and use the composition. Only a single use is required to enable a composition. The composition comprises an immunizing amount of recombinant lipidated High Five cell-produced PsaA or immunogenic fragment thereof, which is taught in the application. The use of High Five cell-produced PsaA or immunogenic fragment thereof as an antigen is taught in the specification and confirmed by the literature cited above. For example, the application teaches that PsaA is a protein antigen from *S. pneumoniae* (see page 4, lines 10-11 and page 6, lines 3 and 4). The application also teaches that native protein antigens such as PsaA, or immunogenic fragments thereof, stimulate an immune response when administered to a host (see page 6, lines 3 and 4). Since the use as an antigen does not require either immunogenicity or a protective immune response, there is no requirement that applicants support these uses. Nevertheless, applicants also provide ample evidence of use as an immunogen and as a protective immunogen (for immunizing) in the application (see Example 3) and the literature reviewed above. Thus, there is no doubt that applicants teach how to make and use the composition of claims 22-24 is provided.

Claims 20-24 are shown above to be enabled in their full scope. Thus, their allowance is respectfully requested.

New Rejections

Rejections Under 35 U.S.C. § 112, Second Paragraph

Claims 27-29

Claims 27-29 are rejected as allegedly indefinite in the recitation of "high five" cells. The Office Action points out that there is support in the specification for "High Five" and "H5" cells, but not for "high five" cells. Applicants have addressed this issue by amending the claims to recite "High Five."

In addition the Office Action states that it is unclear what the identity of the "High Five" or H5 is in the specification, because the term is not defined in the specification. Applicants note that a definition is not required where a term has clear and definite meaning in the art. The term "High Five" has a well known and clear meaning in the art. As evidence of this, applicants submit examples of two PubMed® searches showing that there are at least 58 references that recite "High Five" cells in their abstracts (Exhibits 5-6). Examples of several abstracts (Exhibits 7-16) and 3 full papers (Exhibits 17-19) identified in the PubMed® search are also provided. The fact that this term appears in the abstracts of these publications is significant as it means that "High Five" is not viewed by the skilled person in this field as a term that is indefinite. It is also clear from these references that "High Five" cells are insect cells that are recognized and accepted for use in expression systems for recombinant proteins. Because this is exactly the use of the term "High Five" in the present application, the specification and claims would be viewed by one of skill in the art as having a recognized clear and definite meaning. In the absence of specific evidence to the contrary, applicants' submission of evidence should be accepted as

determinative on the issue of definiteness. Withdrawal of this ground for rejection is believed to be merited and is respectfully requested.

Claims 25-27

Claims 25-27 are rejected as indefinite because it is allegedly not clear whether the phrase ",or immunogenic fragment" refers to the lipoprotein other than PsaA, the mature PsaA or the hybrid protein.

Applicants have amended claim 25 to remove the comma before "or immunogenic fragment." This grammatical change makes the preceding phrase, "a mature PsaA protein" the referent for "or an immunogenic fragment thereof." Thus, the immunogenic fragment is of the mature PsaA. This meaning is supported in the specification at page 9, lines 11-12 which recites "wherein the second sequence encodes a protein portion comprising PsaA, or an immunogenic fragment thereof." In this phrasing, despite the misplaced comma, the only rational interpretation of "or immunogenic fragment thereof" is that it refers to PsaA. By convention in the art and usage in the application, "PsaA" refers to the mature protein. Thus, the amendment is supported and it addresses the issue raised in the Office Action. Withdrawal of this ground for rejection is respectfully requested.

Claims 13-19

Claims 13-19 are rejected as allegedly indefinite because of applicants' use of the term "insubstantial" in the remarks of the previous response. Claim 15 is cancelled, thus mooting this rejection of that claim.

It should be noted, that the term "substantially free" has a well-known and accepted meaning in the art and in the patent law. In fact, there are 17,785 issued U.S. patents that use this term in their claims (see attached set of hits 1-50 from USPTO Patent Full-Text and Image Database search of claims using the term "substantially free" (Exhibit 20)). Examples of claims using this term are also attached (Exhibits 21-22). These uses are consistent with applicants' use of the term. Thus, the term "substantially free" has a clear and definite meaning in the patent law, and is clear and definite in claims 13-19. The term "substantially free" has an understood and accepted meaning in the art as evidenced by the examples of its usage in the literature that are submitted herewith (Exhibits 23-27). There is nothing in applicants' specification, claims or previous response that is inconsistent with the art-recognized meaning. Applicants' statement that the amount of the protein and lipopolysaccharides within the contaminant fraction must be "insubstantial" was intended to convey the same meaning as the accepted and definite meaning of the term "substantially free." The fact that applicants' usage of this term in the argument may have been inaccurate or improper does not change the meaning of the term "substantially free" in the claim. Applicants also stated that the recited protein and lipopolysaccharides are substantially excluded from the contaminant fraction, which is clearly consistent with the well understood meaning of "substantially free." None of applicants' remarks can be construed as making the term "substantially free" unclear, since that term stands for itself in the claims. Thus, the meaning of "substantially free" is the meaning that is understood and accepted as definite in the patent law. Thus, this ground of rejection of claims 13-19 is not supported. Its withdrawal is respectfully requested.

In view of the above amendments and remarks, reconsideration and allowance of the present application are merited and respectfully requested. The Examiner is invited to directly contact the undersigned to discuss any issues relating to the present application.

No fee is believed due. However, the Commissioner is hereby authorized to charge any additional fees which may be required, or credit any overpayment to Deposit Account No. 14-0629.

Respectfully submitted,

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Gwendolyn D. Spratt — Date: 8-19-05